

REMARKS

A. Status of the Claims

Claims 1-31 have been canceled without prejudice to future prosecution. Claim 40 has been amended. Therefore, claims 32-40 are pending after entry of this amendment.

B. Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 32 under 35 U.S.C. §112, second paragraph for recitation of the phrase "sufficient guanidine or amidino moieties." In addition, claim 40 has been rejected as ambiguously reciting dependency from claim 33.

1. *Claim 40 has been Amended to Clarify Dependency*

Applicants have amended claim 40 to depend from claim 32 rather than claim 33. Applicants thank the Examiner for pointing out this typographical error.

2. *The phrase "sufficient guanidine or amidino moieties" is not indefinite*

The Examiner has rejected claim 32 for the recitation of the phrase "sufficient guanidine or amidino moieties." The Examiner alleges that the phrase renders claim 32 unpatentable under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the invention. More specifically, the Examiner alleges that Applicants have not recited the desired amount of guanidine or amidino residues.

Applicants respectfully disagree because 35 U.S.C. §112, second paragraph does not require that claim 32 specify desired amounts of guanidine or amidino residues where one of skill could easily determine the number of guanidine or amidino residues "*sufficient ... to increase* the delivery of the biologically active agent across a biological barrier." See claim 32.

The Federal Circuit has held that the use of the term "sufficient to increase" does not render a claim indefinite where one of skill in the art could easily determine the metes and bounds of the claim. See *Exxon Research and Engineering Co. v. United States*, 265 F.3d 1371, 60 USPQ2d 1272 (Fed. Cir. 2001); 54 USPQ2d 1519. In *Exxon Research*, the claim at issue was drawn to a method of activating cobalt with a catalyst. The claim included an element requiring:

[T]reating the catalyst with hydrogen or a hydrogen containing gas in the presence of hydrocarbon liquids for a period *sufficient to increase* substantially the initial catalyst productivity *See Exxon Research* at 1275.

In overturning the District Court's finding of indefiniteness, the Federal Circuit held that:

Although the patent does not quantify the "period sufficient" limitation by reference to any specific period or range of periods, it does not leave those skilled in the art entirely without guidance as to the scope of that requirement ... *[I]t appears that one of skill in the art could measure the period "sufficient to increase* substantially the initial catalyst activity" for a particular catalyst more precisely by conducting activity checks ... Provided that the claims are enabled, and no undue experimentation is required, *the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite* (citing *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316(Fed. Cir. 1983)). *See Exxon Research* at 1279.

Therefore, 35 U.S.C. §112, second paragraph does not require recitation of specific quantities where one of skill in the art can easily determine the scope of the claim.

The present issue is similar to that in *Exxon Research*. Applicants submit that one of skill in the art could easily determine the desired number of guanidine or amidino moieties based on the teachings in the specification. For instance, Applicants specifically disclose two methods of measuring "the delivery of the biologically active agent across a biological barrier." In Example 1, Applicants demonstrate that a fluorescent dye may be used to asses the ability of the transporter to assist in cellular uptake. *See Example 1, Figure 2 and Figure 3.* In Example 3, Applicants demonstrate that a standard cytotoxicity assay may be used to assess the ability of the transporter to increase delivery of a drug. *See Example 3 and Figure 5.*

In addition to providing specific assays, Applicants provide specific numbers of guanidino and/or amidino moieties that may be "sufficient ... to increase the delivery of the biologically active agent across a biological barrier." For example, on page 11, lines 5-6, Applicants state that "[t]he delivery-enhancing transporters typically include 6 to 50 guanidino

and/or amidino moieties, more preferably between 7 and 15 such moieties." After examining this passage, one skilled in the art would begin with between 7 and 15 guanidino and/or amidino moieties in determining the number of guanidino and/or amidino moieties "sufficient ... to increase the delivery of the biologically active agent across a biological barrier."

Because one skilled in the art could easily assess the number of guanidine and/or amidino moieties sufficient to increase the delivery of a biologically active agent across a biological barrier, Applicants submit that claim 32 satisfies §112, second paragraph. Therefore, Applicants respectfully request withdrawal of the rejection.

C. Rejection Under 35 U.S.C. §102(b)

The Examiner has rejected claims 32 and 40 under 35 U.S.C. §102(b) as allegedly anticipated by Sumner-Smith *et al.* (Canadian Patent App. 2,094,658) (hereinafter referred to as "Sumner-Smith"). The Examiner characterizes Sumner-Smith as disclosing a coupled carrier peptide preferably consisting of eight or nine arginine residues. The Examiner asserts that the coupled carrier peptide anticipates Applicants' composition comprising a biologically active agent, a delivery-enhancing transporter having guanidino/amidino moieties, and a pharmaceutically acceptable carrier.

Applicants respectfully disagree because Sumner-Smith discloses a *coupled* carrier peptide *conjugate* whereas Applicants' invention is a *composition* containing a distinct, unconjugated delivery-enhancing transporter.

As the Examiner is aware, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See* MPEP § 2131 (quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). Sumner-Smith fails to expressly or inherently describe all of the elements set forth in claims 32. Claim 32 recites "[a] *composition* comprising" three distinct elements: "a biologically active agent;" "a delivery-enhancing transporter;" and "a pharmaceutically acceptable carrier." *See* claim 32. Sumner-Smith discloses the use of "a chemical *conjugate* comprising the biochemical agent and a carrier peptide coupled chemically therewith." *See* page 3, lines 1-2. Therefore, Sumner-Smith fails to describe a "delivery-

"enhancing transporter" that is a distinct, unconjugated component of a *composition*, as recited in claim 32.

Applicants have emphasized throughout the written description that the delivery-enhancing transporter is a distinct, unconjugated component of the composition. An exemplary composition is described at page 10 lines 15-21:

In one group of embodiments, the present invention provides a composition of a delivery-enhancing transporter and a biologically active agent. The composition is a *non-covalent* combination of the delivery-enhancing transporter and the biologically active agent. Rather than a covalent composition, the components are held in an ionic association, typically viewed as an ion pair. Despite the term "ion pair," the invention will, in some embodiments, include compositions of one or more biologically active agents in association with one delivery-enhancing transporter [emphasis added].

Further descriptions of the distinct, unconjugated nature of Applicants' delivery-enhancing transporter can be found at page 23, lines 9-12 (stating "[d]erivatized biological agents can then be combined with a suitable delivery-enhancing transporter to form a *non-covalently* bound complex which is suitable to delivery of the biological agent *in vivo*"); page 25, lines 3-6 (stating "[i]n one preferred embodiment, the agent is combined with a single delivery-enhancing transporter to form a composition which is thought to exist as a *non-covalently* bound ion pair"); Figure 2, and Examples 1-3.

In addition to describing the distinct, unconjugated nature of the delivery-enhancing transporter, Applicants have presented experimental results demonstrating the advantages of the claimed composition over a covalent conjugate. In Example 1, Applicants compared the cellular uptake of fluorescein using an unconjugated polyarginine transporter versus a fluorescein-polyarginine conjugate. On page 34, line 27, to page 35, line 4, the following results are reported:

However, the staining pattern of the cells was fundamentally different when compared to fluorescein that was covalently attached to short polymers of arginine (see Figure 4). Distinct punctate staining was seen on the cell

surface as well as in the cytosol, when covalent conjugates were used (data not shown). More importantly, staining of individual cells was very heterogeneous, with the variation in cell fluorescence ranging over three orders of magnitude. In contrast, when *noncovalent* conjugates were used, cell staining was *remarkably uniform* with cell fluorescence varying only by a factor of 2-4. The staining was *extremely intense*, with the majority of the dye being on the cell surface (see Figure 4) [emphasis added].

Thus, Applicants report that a composition comprising a fluorescein and a distinct, unconjugated delivery-enhancing polyarginine transporter results in more uniform and more intense cell fluorescence than a fluorescein-polyarginine conjugate.

Therefore, because Sumner-Smith fails to describe a "delivery-enhancing transporter" that is a distinct, unconjugated component of a *composition* as recited in claim 32, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. §102(b).

D. Rejection Under 35 U.S.C. §103(a)

The Examiner has rejected claims 32, 33 and 40 under 35 U.S.C. §103(a) as allegedly obvious over Katz *et al.* (United States Patent No. 6,005,004) (hereinafter referred to as "Katz"). The Examiner characterizes Katz as disclosing a delivery system comprising a biologically active agent, a transporter agent, and a pharmaceutically acceptable carrier. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Katz and generate Applicants' composition as claimed.

Applicants respectfully disagree because Katz describes a *conjugate* containing a therapeutic agent *covalently bonded* to a cationic carrier whereas Applicants' invention is a composition containing a distinct, *unconjugated* delivery-enhancing transporter. See Abstract of Katz (stating "[t]he complexes are further *covalently bonded* with cationic carriers and permeabilizer peptides for delivery across the blood-brain barrier....").

Applicants respectfully submit that the Examiner has not set forth a *prima facie* case of obviousness. In order to establish a *prima facie* case of obviousness, the rejection must

demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully assert that Katz does not teach all the claimed elements. Claim 32 recites "[a] composition comprising" three distinct elements: "a biologically active agent;" "a delivery-enhancing transporter;" and "a pharmaceutically acceptable carrier." *See* claim 32. Katz describes the use of "site-specific bimolecular lipophilic complexes, also called conjugates ... said complex is conjugated with cationic carriers to enhance its passage from the blood circulation to the brain." *See* column 1, lines 9-15. Therefore, Katz fails to teach or suggest a "delivery-enhancing transporter" that is a distinct, unconjugated component of a composition, as recited in claim 32. As described above, Applicants have emphasized throughout the written description that the delivery-enhancing transporter is a distinct, unconjugated component of the composition. *See*, for example, page 10 lines 15-21; page 23, lines 9-12; page 25, lines 3-6. In addition, Applicants have presented experimental results demonstrating the advantages of the claimed composition over a covalent. *See* Example 1.

Because Katz fails to teach or suggest a "delivery-enhancing transporter" that is a distinct, unconjugated component of a composition as recited in claim 32, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. §103(a).

E. Double Patenting Rejection

The Examiner has provisionally rejected claim 32 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 30 of copending Application No. 09/957,161; claims 1-10 of copending Application No. 09/083,259; and claims 1-7 and 18 of copending Application No. 09/396,195. Applicants respectfully disagree.

Applicants first note that Application No. 09/957,161 has been abandoned. A double patenting issue may not be raised between a pending application and an abandoned

application. *See MPEP § 804.* Therefore, Applicants request withdrawal of the double patenting rejection as being unpatentable over claims 1 and 30 of Application No. 09/957,161.

In addition, the Examiner is respectfully reminded that the test for determining patentability under the judicially created doctrine of obviousness-type double patenting is whether the claims in the application define an invention that is merely an obvious variation of an invention claimed in the patent. Applicants respectfully submit that claim 32 is not merely an obvious variation over the claims of Application No. 09/083,259 (now United States Patent No. 6,306,993) and Application No. 09/396,195 (now United States Patent No. 6,495,663) because none of the claims cited by the Examiner suggest a distinct, unconjugated delivery-enhancing transporter component of a composition as recited in claim 32 of the present application.

All of the cited claims are limited to transport peptides that are *covalently attached* to biologically active agents. Application No. 09/083,259, now United States Patent No. 6,306,993, contains 15 claims. Claim 1, the only independent claim, recites:

1. A composition for delivering paclitaxel across a biological membrane, comprising:
a conjugate containing paclitaxel *covalently attached* via a linker that is cleavable in vivo to a transport peptide, wherein said peptide consists of from 6 to 25 amino acid residues, at least 50% of which contain a guanidino or amidino sidechain moiety, and contains at least 6 contiguous guanidino and/or amidino sidechain moieties,
whereby said attached transport peptide is capable of delivering said paclitaxel across a biological membrane

(emphasis added). Thus, claim 1 of United States Patent No. 6,306,993 claims "[a] composition" comprising one distinct element: "a conjugate containing paclitaxel *covalently attached* ... to a transport peptide." Application No. 09/396,195, now United States Patent No. 6,495,663, contains 18 claims. Claim 1, the only independent claim, recites in relevant part:

1. A conjugate for administration, to a mammalian subject, of an antimicrobial agent whose efficacy in non-conjugated form is limited by its solubility in aqueous liquid or its inability to cross biological membranes to manifest biological activity, said conjugate comprises a transport

peptide **covalently attached** by a linker to the antimicrobial agent, said linker being cleaved in vivo to release the antimicrobial agent from the linker and the transport peptide ...

(emphasis added). Thus, claim 1 of United States Patent No. 6,495,663 claims "[a] conjugate" comprising "a transport peptide **covalently attached** by a linker to the antimicrobial agent."

As described in detail above, Applicants have emphasized throughout the written description that the delivery-enhancing transporter is a distinct, **unconjugated** component of the composition. *See*, for example, page 10 lines 15-21; page 23, lines 9-12; page 25, lines 3-6. In addition, Applicants have presented experimental results demonstrating the advantages of the claimed composition over a covalent conjugate. *See Example 1.*

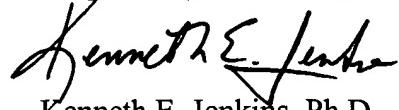
Therefore, because the claims of United States Patent No. 6,495,663 and United States Patent No. 6,306,993 fail to suggest a "delivery-enhancing transporter" that is a distinct, unconjugated component of a composition as recited in claim 32, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. §103(a).

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for examination. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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